

wherein the first end of the second tube is positioned near the bottom of the second container, the second end of the second tube is positioned at or above the third container;

a computer-controlled pressure-altering device, attached to the housing in a pressure-tight manner, that changes the pressure within said housing relative to the pressure outside the housing;

a vacuum device that draws liquid through the second tube;

wherein the pressure-altering device applies a pressure differential that causes liquid to be transferred through the capillary tubes from a container selected from the group consisting of the first container and the second container.

REMARKS

Applicants have studied the Office Action of March 15, 2000 ("Office Action"), and have made amendments to the claims. It is respectfully submitted that the application, as amended, is in condition for allowance. Claims 1-14 are pending in the present application. Claims 1-3, 6, 9-11, and 14 have been amended. Claims 4, 5, 7, and 8 have been cancelled. Claims 15-30 are withdrawn from consideration. Claims 31-35 have been added. No new matter has been added. Reconsideration and allowance of the claims in view of the above amendments and the ensuing remarks are respectfully requested.

Claim 1 has been amended to more specifically define that which Applicants regard as their invention. Amended claim 1 is now drawn to a liquid-handling system comprising a first container, a second container, a pressure-tight housing that encases

the first container, a capillary tube extending between the first and second containers, and a computer-controlled pressure-altering device used to drive liquid through the capillary, between the first and second containers. Support for this amendment can be found in the Specification at page 8, lines 4-7, 9-15, 21-23 and 25-27, at page 10, lines 1-2, and in Fig. 1, No. 101.

Claim 2 has been amended to more specifically define that which Applicants regard as their invention. Amended claim 2 is now drawn to the system of claim 1 wherein the capillary tube is sealed through the wall of the housing in a pressure-tight manner. Support for this amendment can be found in the Specification at Fig. 3, Nos. 115 and 117.

Claim 3 has been amended to more specifically define that which Applicants regard as their invention. Amended claim 3 requires the computer-controlled pressure-altering device of claim 1 to be a vacuum source. Support for this amendment can be found in the Specification at page 13, lines 6-8 and 13-17.

Claims 4 and 5 have been cancelled.

Claim 6 has been amended to remain in proper dependent claim format.

Claims 7 and 8 have been cancelled.

Claim 9 has been amended to more specifically define that which Applicants regard as their invention. Support for this amendment can be found in the Specification at page 9, lines 9-13.

Claim 10 has been amended to more specifically define that which Applicants regard as their invention. Amended claim 10 refers to the particular sources of pressurized gas suitable for use with the computer-controlled pressure-altering device

of claim 1. Support for this amendment can be found in the Specification at page 8, lines 21-23.

Claim 11 has been amended to more specifically define that which Applicants regard as their invention. Support for this amendment can be found in the Specification at page 13, lines 6-8 and 13-17.

Claim 14 has been amended to more specifically define that which Applicants regard as their invention. Support for this amendment can be found in the Specification at page 13, lines 12-16.

Claim 31 is drawn to the liquid-handling system of claim 6, further comprising manifolds to properly position the capillaries relative to the first and second containers. Support for this amendment can be found in the Specification at page 8, lines 7-8 and 18-20.

Claim 32 is drawn to a liquid-handling system for transferring liquid between containers, wherein at least two capillaries terminate at separate containers at one of their ends, and at one single container at their opposite end. Support for this amendment can be found in the Specification at page 10, lines 17-23.

Claim 33 is drawn to the liquid-handling system of claim 32, wherein two capillaries terminate at a single second container. Support for this amendment can be found in the Specification at page 10, lines 17-23.

Claim 34 is drawn to the liquid-handling system of claim 32, wherein the system comprises a plurality of first containers and a plurality of second containers. Support for this amendment can be found in the Specification at page 8, lines 4-7 and 18-20.

Claim 35 is drawn to a liquid-handling system wherein liquid is transferred among three different containers, through at least two capillaries. Support for this amendment can be found in the Specification at page 13, lines 12-20.

The present invention is directed to a microplate sample and reagent loading system, and a method of performing the same. There is described a liquid-handling apparatus for forward and reverse transfer of fluids through capillaries, such that applied pressure differentials effectuate such transfers uniformly and in parallel. There are further described several configurations of liquid-handling systems. There is still further described a method for accurately controlling a desired volume of fluid flow, especially useful when multiple liquid wells require identical volumes of liquid to be deposited therein or removed therefrom.

In the Office Action, Examiner required Applicants to restrict the further prosecution of their application to either claims 1-14 (Group I) or claims 15-30 (Group II) under 35 U.S.C. §121, asserting that the apparatus as claimed can be used to practice another and materially different process. In a telephone conversation between Mr. Joel German and the Examiner on February 14, 2000, Applicants made a provisional election with traverse to prosecute the invention of Group I. At this time, Applicants respectfully affirm the provisional election to prosecute the invention of Group I, and therefore withdraw from consideration claims 15-30 (Group II). This requirement for restriction remains respectfully traversed.

The apparatus of the instant invention can be used to practice no process materially different from that specified in claims 15-30. In the Office Action, Examiner asserts that the apparatus as claimed can be used for the separation of biomolecules by

capillary electrophoresis. However, the apparatus of the instant invention as claimed is by itself unable to perform capillary electrophoresis. Such a process requires the presence of many components that are not a part of the instant invention. For instance, there is neither a power source nor an indication of a corresponding voltage potential indicated anywhere in the claims of the instant invention. Without such elements, electrophoresis can not be performed.

In light of the foregoing remarks, and since examining claims 1-14 and 15-30 together would not create an undue burden, Applicants respectfully submit that restriction of their application is improper. As Examiner has cited no materially different process that can be practiced with the apparatus of the instant invention, withdrawal of the requirement for restriction under 35 U.S.C. §121 is respectfully requested.

In the Office Action, Examiner objected to the drawings under 37 CFR 1.83(a) as not showing every feature of the invention specified in the claims. Specifically, the Examiner stated that claims 7 and 8 made reference to a "translation system means" that was not depicted in the drawings. Relevant claims 7 and 8 have been cancelled. As these features no longer appear in the claims, it is respectfully submitted that the drawings are now in proper form.

In the Office Action, Examiner further noted that the specification was missing a description of Figs. 4a-b and 6a-c in the Brief Description of the Figures section. The Brief Description of the Figures Section has been amended to more specifically describe the content of the figures, making detailed reference to each and every portion thereof. It is therefore respectfully submitted that the Brief Description of the Figures section is now in proper form.

In the Office Action, Examiner further rejected claims 1-14 under 35 U.S.C. §112, first paragraph, as not being enabling with regard to Applicant's various "translation subsystem means." Claims 7-8 have been cancelled, and are the only claims that make any reference to such "translation subsystem means." As Applicants no longer claim the use of any such "translation subsystem means," it is respectfully submitted that remaining claims 1-3, 6, and 9-14 are now in proper form under 35 U.S.C. §112, first paragraph.

In the Office Action, Examiner further rejected claims 1-14 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner stated that Claim 1 was unclear as to what "two ends" referred to. In claim 3, use of the phrase "intrinsic and extrinsic" with respect to the vacuum source was vague and indefinite. The Examiner stated that Claims 7 and 8 were vague and indefinite for "translation subsystem means" language, and stated that Claim 9 was unclear as to whether it was the capillary tube or another element that was made from the group comprising polyamide, polyethylene, polypropylene, etc. Finally, the Examiner stated that, in claim 14, the phrase "at least one of sequential and parallel transport" was unclear.

Amended claim 1 now more accurately describes that which Applicants consider their invention. Reference to "two ends" has been deleted having been replaced with the more descriptive terms "first end" and "second end." The first end and second end of Applicants' invention refer to the two opposing endpoints of the capillary tube(s) used in the embodiments of the present invention. As the language of claim 1 is no longer unclear, it is respectfully submitted that claim 1 is now in proper form under 35 U.S.C. §112, second paragraph, and withdrawal of the rejection is respectfully requested.

Amended claim 3 now more accurately describes that which Applicants consider their invention. Reference to any "intrinsic and extrinsic" vacuum source has been deleted. Claim 3 now solely refers to "*a vacuum source.*" As the language of claim 3 is no longer vague and indefinite, it is respectfully submitted that claim 3 is now in proper form under 35 U.S.C. §112, second paragraph, and withdrawal of the rejection is respectfully requested.

As claims 7 and 8 have been cancelled, it is respectfully submitted that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

Amended claim 9 now more accurately describes that which Applicants consider their invention. The elements of the Markush group have been rearranged such as to remove any grammatical ambiguity therefrom. While the external coating of the pulled glass tubes may be fabricated from some of the elements of the group, these same elements can alternatively provide the material basis for a capillary tube. As this latter meaning is now clearly depicted in the language of amended claim 9, it is respectfully submitted that claim 9 is in proper form under 35 U.S.C. §112, second paragraph, and withdrawal of the rejection is respectfully requested.

Amended claim 14 now more accurately describes that which Applicants consider their invention. The phrase "at least one of sequential and parallel transport" has been deleted. Claim 14 now refers to the system of claim 1 with the added limitation of an individual container having multiple capillaries residing therein. As the language of claim 14 is no longer unclear, it is respectfully submitted that claim 14 is now in proper form under 35 U.S.C. §112, second paragraph, and withdrawal of the rejection is respectfully requested.

In the Office Action, Examiner further rejected claims 1-10 under 35 U.S.C. §102(b) as being anticipated by Panussis et al. (*A Pneumatic Device for Rapid Loading of DNA Sequencing Gels*) ("Panussis"). This rejection is respectfully traversed.

For a reference to properly anticipate a patent application under 35 U.S.C. §102(b), the reference must have been published *more than one year prior to the date of application for patent* in the United States. Panussis was first published in the scientific journal *Genome Research* in May 1998. The filing date of the present application is November 15, 1998. Thus, the reference does not anticipate Applicants' invention under 35 U.S.C. §102(b), as its date of publication does not predate the filing date of the instant application by more than one year. Furthermore, Applicants do not in any way accept the subject matter relied on in Panussis as prior art, and the discussion contained herein should not be construed as an implicit adoption thereof.

In light of the foregoing remarks, Applicants respectfully submit that Panussis cannot anticipate any of the pending claims under 35 U.S.C. §102(b). Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Applicants have recently become aware of U.S. Patent No. 5,849,598 to Wilson et al. ("Wilson"), a copy of which is included with this Amendment as per the Supplemental Information Disclosure Statement being filed herewith.

Wilson teaches a method for transferring micro quantities of liquid samples from a first plurality of cells to a second plurality of corresponding cells. Col. 3, Ins. 35-41. In this rigid system, the first and second plurality of cells is related in a fixed, one-to-one manner. In preferred embodiments, the electrophoresis gel loading apparatus of Wilson is particularly suited for two test tube racks each containing 32 tubes connected by 32

capillaries to 32 corresponding cells in a an electrophoresis gel. Col. 4, Ins. 53-56, and 61-64, Col. 5, Ins. 52-55, and Fig. 7. The pressure gradient sustained in the apparatus of Wilson is controlled manually, preferably by a hand pump. Col. 5, Ins. 1-3.

The instant invention is directed to a liquid-handling system that provides a wide variety of configurations with respect to the number of containers among which liquid is transferred, as well as the manner in which these containers are related to one another. Moreover, as depicted in amended claim 32, the instant invention includes a system in which several capillaries have one end in separate containers, yet terminate at their other end in the same container, allowing for several different liquids to be transferred to the latter, in parallel. Conversely, this same system can be used to draw liquid out of one container into several different containers. Finally, another embodiment of the instant invention, described in amended claim 35, provides for a system with a third container, such that liquid can be transferred between the first and second containers in either direction, and with any suitable arrangement of capillaries, but can be further transferred from the second container to the third container.

Flexibility of design is key in the instant invention, and is taught neither in the loading apparatus of Wilson, nor in the methods disclosed therein. Wilson does not describe or suggest the multiple combinations of containers and capillaries that are at the core of the instant invention. In fact, owing to the fixed nature of the bores through which capillaries must pass in the apparatus of Wilson, combining multiple capillaries in a single well would not be readily feasible. Yet, this very embodiment is part of Applicants' invention at independent claim 32, wherein the system has at least two capillary tubes, whose first ends are "...positioned near the bottom of said first

container.” Clearly, Wilson is directed to a system with a specific set of test tubes related by a set of capillaries to a corresponding plurality of cells in an electrophoresis gel. Furthermore, Wilson does not teach the addition of a third container as recited in the instant invention in independent claim 35, wherein the “...second end of the second tube is positioned at or above the third container.” The loading apparatus of Wilson allows only for two sets of containers.

Moreover, the pressure differential in the gel loading apparatus of Wilson is controlled by a hand pump. Wilson describes the potential for other sources of pressure to be employed, such as an electric pump or pressurized gas cylinder, yet it appears that these are all to be controlled manually. Col. 5, Ins. 35-41. Quite to the contrary, in all independent claims of the instant invention, Applicants’ source of pressure is “a computer-controlled pressure-altering device.” To ensure that precise quantities of liquid are transferred in accordance with their invention, Applicants’ use such a pressure source, rather than the less exacting, manually-operated devices.

In the Office Action, Examiner further rejected claims 1-10 under 35 U.S.C. §102(b) as being anticipated by Webb (U.S. Patent No. 4,621,665). This rejection is respectfully traversed.

Webb teaches a method and apparatus for simultaneously filling the wells on a microbeaker plate by forcing air through a set of capillaries into a set of vessels which, in turn, causes liquid to fall out of the vessels into corresponding wells. Col. 4, In. 63 through Col. 5, In. 7. The amount of liquid that remains in each well is determined by the height of the dispensing vessel above the well, since excess liquid that falls into the well is sucked back into the vessel after pressure is released from the device. Col. 5,

Ins. 8-19. The Webb device is fixed in such a manner that liquid falls from one specific vessel to one corresponding specific microbeaker. Fig. 1, Nos. 2 & 3.

The present invention provides a liquid-handling system for transferring liquid back and forth between separate containers wherein liquid is caused to migrate between the two containers due to a pressure differential. The liquid is transported through at least one capillary tube, and the determination of the appropriate pressure depends upon calculations that necessitate use of capillaries of predetermined length and internal diameter. The present invention further provides a wide variety of possible combinations with respect to the configuration of capillaries and the number of containers related thereby, as multiple capillaries can reside, for example, in one single container, yet the opposing ends of these same capillaries can reside in multiple containers.

As stated in Applicants' independent claims 1, 32, and 35, the capillaries of the instant invention are conduits for a liquid which is deposited or removed from a container or set of containers in precise quantities due to the use of a pressure source. Deposit and/or removal are effectuated by forcing the *liquid* to travel "*through said...capillary tubes.*" In marked contrast, the device of Webb provides a system for transporting *air* through a set of capillaries that causes liquid to be expelled from a set of vessels. Col. 4, ln. 63 through Col. 5, ln. 7.

This distinction in construction highlights the completely different manner in which the devices of the instant invention and that of Webb function. The device of Webb deposits an equal amount of liquid in each of several wells by forcing more liquid than is appropriate into the wells, and then sucking the excess liquid out. Col. 5, Ins. 8-

15. As such, the device of Webb does not provide for a sustained pressure differential.

not
in claims

Rather, the amount of remaining liquid depends entirely on the distance between the end of the depositing vessel and the bottom of the well. Col. 5, Ins. 16-19. Quite to the contrary, in delivering precise quantities of a liquid from one container to another, the instant invention functions entirely independently of the distance between the second end of the capillary and the bottom of the second container. This is due to the fact that the amount of liquid deposited is governed by a sustained pressure differential, in accordance with Applicants' claim 1, and, once this pressure is achieved it need not be further changed to reach the desired liquid volume in a second container.

Furthermore, the device of Webb does not teach a manifold for holding and spacing the capillary tubes as does the instant invention. The capillaries of Webb terminate at one end in a fitted manner to a liquid-containing vessel and at the opposing end in a fitted manner to an air-containing vessel. Fig. 2, Nos. 1 & 11, and Fig. 4, Nos. 11 & 17. The capillaries of the present invention, however, are not attached at either end. Rather, the instant invention utilizes a first and second manifold that merely hold the capillaries in place over their respective containers, but these manifolds do not receive or transmit liquid. As recited in Applicants' claim 31, each manifold "*holds...at least one capillary tube.*"

In light of the foregoing remarks, Applicants respectfully submit that Webb does not anticipate any of the pending claims. Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

In the Office Action, Examiner further rejected claims 1-6 under 35 U.S.C. §102(e) as being anticipated by Kernan et al. (U.S. Patent No. 5,885,430) ("Kernan"). This rejection is respectfully traversed.

Kernan teaches an electrophoretic apparatus that provides a system for simultaneously introducing samples of macromolecules into a plurality of capillaries. Though pressure may be applied to partially load samples into one end of the capillaries, such pressure is not used to deliver these samples completely through the capillaries to a container at the opposing end. Rather, once loaded, a voltage differential causes macromolecular samples to migrate through gel in the capillaries. Moreover, a pump may be utilized to force gel or other solutions into the capillaries, but this pump is not used to completely deposit liquid into containers at the opposing ends of the capillaries. Instead, much of the material to be pumped is lost through an outlet in the system rather than proceeding through the capillaries. Col. 12, Ins. 52-66. Furthermore, the apparatus of Kernan does not provide for bi-directional liquid flow. ①

As required by claim 1, the instant invention is a liquid-handling system used to transfer liquid back and forth between two containers. To accomplish this goal, capillaries are employed as conduits for various liquids, and pressure is the driving force that causes liquid to flow from at least one first container through at least one capillary into at least one second container. Also, as detailed in claim 1, the system of the instant invention is capable of transferring liquid back and forth, allowing for bi-directional flow.

Applicants' invention is readily distinguishable from the apparatus of Kernan in two basic fashions. First, as described in Applicants' claim 1, the instant invention

utilizes pressure to transfer liquid from at least one first container *entirely* through at least one capillary into at least one second container. The apparatus of Kernan, however, is used to pump gel into a set of capillaries through which macromolecules will later travel once a voltage differential is applied, but is not used to transport this gel *through* the capillaries, from one receptacle into another. Moreover, the apparatus of Kernan does pump acid or base solution through the capillaries to clean them after electrophoresis is performed, but in doing so, a pump is employed wherein the end of the capillaries proximal to the pump is not positioned near the bottom of the first container. Fig. 8, Nos. 374 & 382. To the contrary, claim 1 of the instant invention requires that the first end of the capillaries be located "*near the bottom of said first container*", else Applicants' system would not be capable of transporting all of the liquid in one of its first containers into and through the capillaries. This is not needed for the apparatus of Kernan, as that apparatus does not transport nearly all of the solution, as is evidenced by the fact that a great deal of any acid or base solution will pass through Kernan's interior cavity (Fig. 8, No. 374) and out through the outlet (Fig. 8, No. 358) and not through the capillaries (Fig. 8, No. 382). Finally, in one embodiment Kernan forces the movement of liquid by creating a pressure differential, but this is used only to force electrophoresis samples "*slightly*" into the capillary ends, at which point any pressure differential is eliminated. In fact, the apparatus of Kernan would not function correctly if these samples were forced entirely through the capillaries, as electrophoresis could not then be performed as described therein.

Second, an important feature of the instant invention is its ability to perform bi-directional flow. Pressure is used, in the instant invention, to force liquid from at least

one first container through at least one capillary to at least one second container, *or the reverse*, by simply applying different levels of pressure. Kernan does not contemplate this feature of the instant invention, which appears in Applicants' claim 1, wherein *"...liquid contained in either the first container or the second container [is] transferred through the capillary tube."*

In light of the foregoing remarks, Applicants respectfully submit that Kernan does not anticipate any of the pending claims. Withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

In the Office Action, Examiner further rejected claims 11-13 under 35 U.S.C. §103(a) as being obvious in light of Panussis. This rejection is respectfully traversed.

Panussis has been cited by the Examiner as a prior art reference solely under 35 U.S.C. §102(b), yet, as stated above, Panussis is not a valid prior art reference thereunder. Thus, Panussis can not form the basis of a rejection under 35 U.S.C. §103, as that statute requires a reference to first be deemed prior art under a section of 35 U.S.C. §102. *Panduit Corp. v. Dennison Mfg. Co.*, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Furthermore, Applicants reiterate that they do not in any way accept the subject matter relied on in Panussis as prior art, and the discussion contained herein should not be construed as an implicit adoption thereof. *In re Hellsund*, 177 USPQ 170 (C.C.P.A. 1973).

In light of the foregoing remarks, Applicants respectfully submit that Panussis can not render any of the pending claims obvious, as the reference does not qualify as valid prior art under 35 U.S.C. §102(b). Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Applicants take note of Examiner's comments with regard to joint inventorship concerns both in terms of amending inventorship upon cancellation of claims following election under 37 CFR 1.48(b), as well as obligations under 37 CFR 1.56 to indicate inventor and invention dates of each claim without common ownership. However, inventorship has not changed as a result of the restriction requirement, and, moreover, the pending claims are rightly attributed to collaborative efforts.

Applicants believe the foregoing amendments place the application in condition for allowance. Early, favorable action is respectfully requested.

If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 488-7100 to discuss the steps necessary for placing the application in condition for allowance.




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Respectfully submitted,

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